DRUG INFORMATION ASSOCIATION

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Implementation of Quality-by-Design: Question-based Review

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Generic Drugs Hit Backlog At FDA

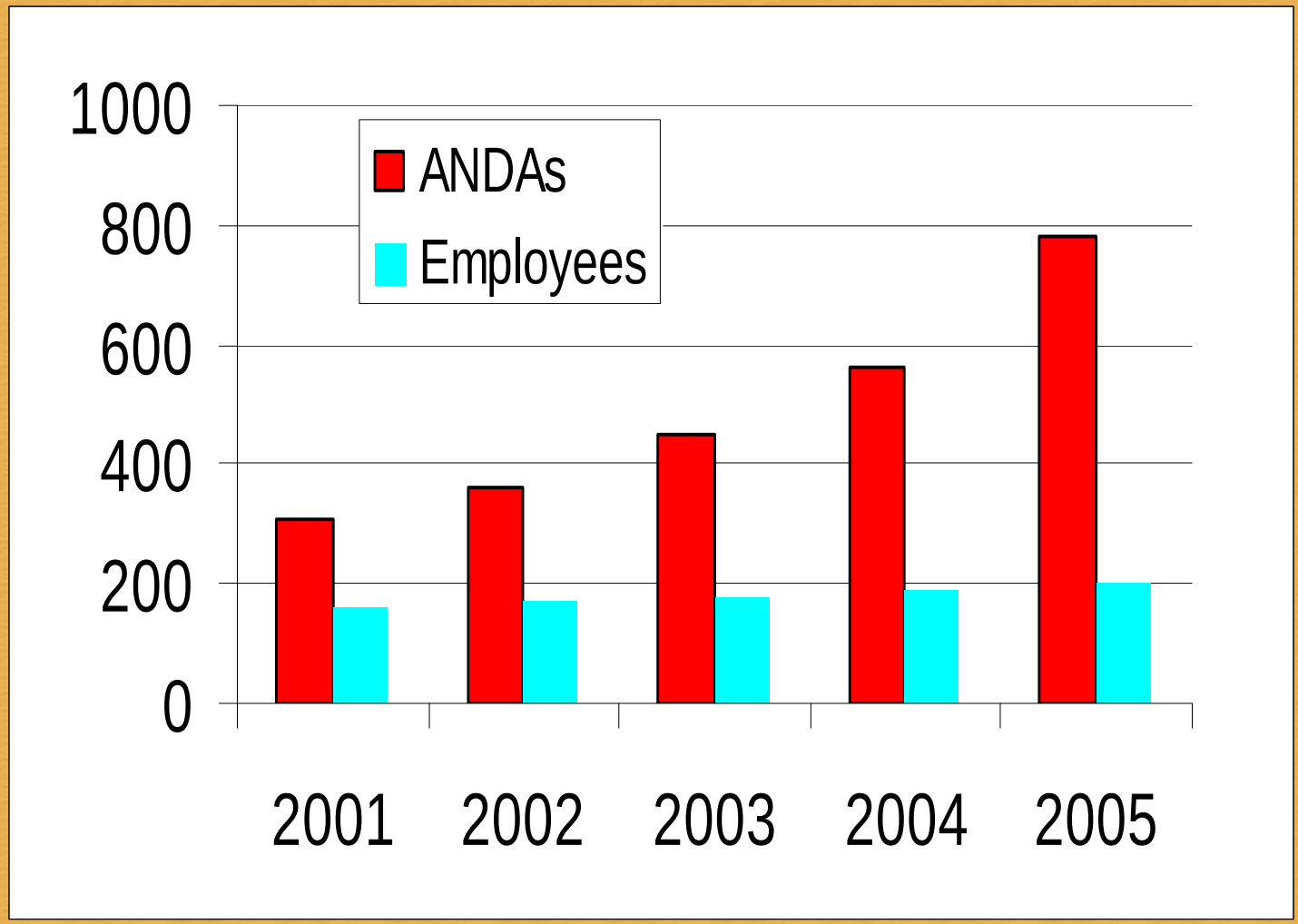
No Plans to Expand Review Capabilities

By Marc Kaufman
Washington Post Staff Writer

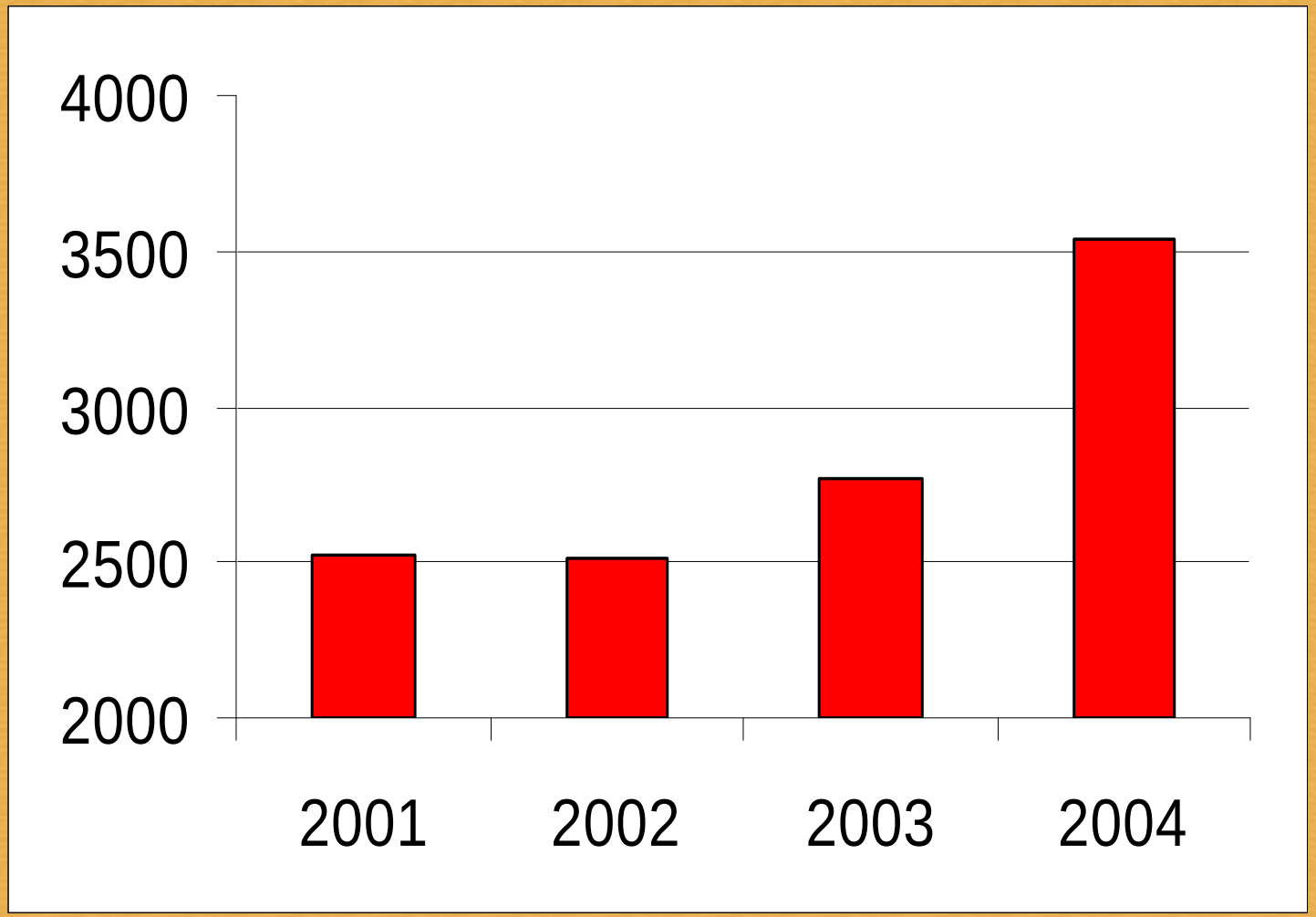
" …the Food and Drug Administration has a backlog of more than 800 applications to bring new generic products to the market - an all-time high."

"Rep. Henry A. Waxman (D-Calif.), 'This is the time for the FDA to be ramping up its generic reviews, not to be falling so badly behind.'"

Receipts of ANDAs



Receipts of Supplements (ANDAs)



The Desired State: A Mutual Goal of Industry, Society, and the Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight

Pharmaceutical Quality in the 21st Century
Janet Woodcock, M.D.
Deputy Commissioner for Operations

Characteristics of Desired State

- Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
- Manufacturers strive for continuous improvement
- FDA role: Initial verification, subsequent audit
- No manufacturing supplements needed

Pharmaceutical Quality in the 21st Century
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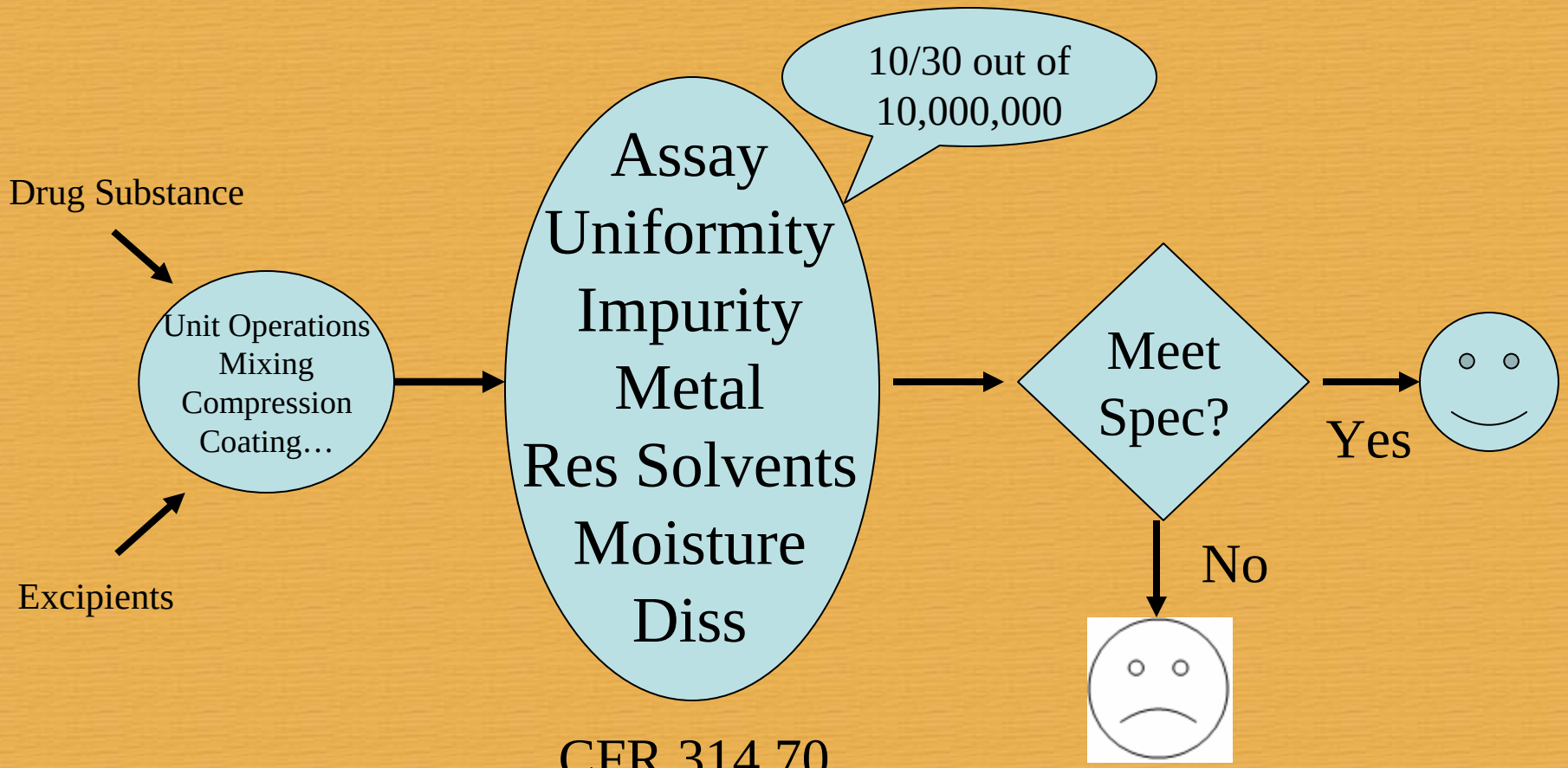
Current CMC Review: Issues

- Quality by end product testing
  - Little or no scrutiny on product and process design
- Product specifications
  - Little or no mechanistic understanding
  - “Overly conservative and often irrelevant specifications”
- Does not adjust review to the level of scientific understanding

Quality by End Product Testing



CFR 314.70
Change Guidance

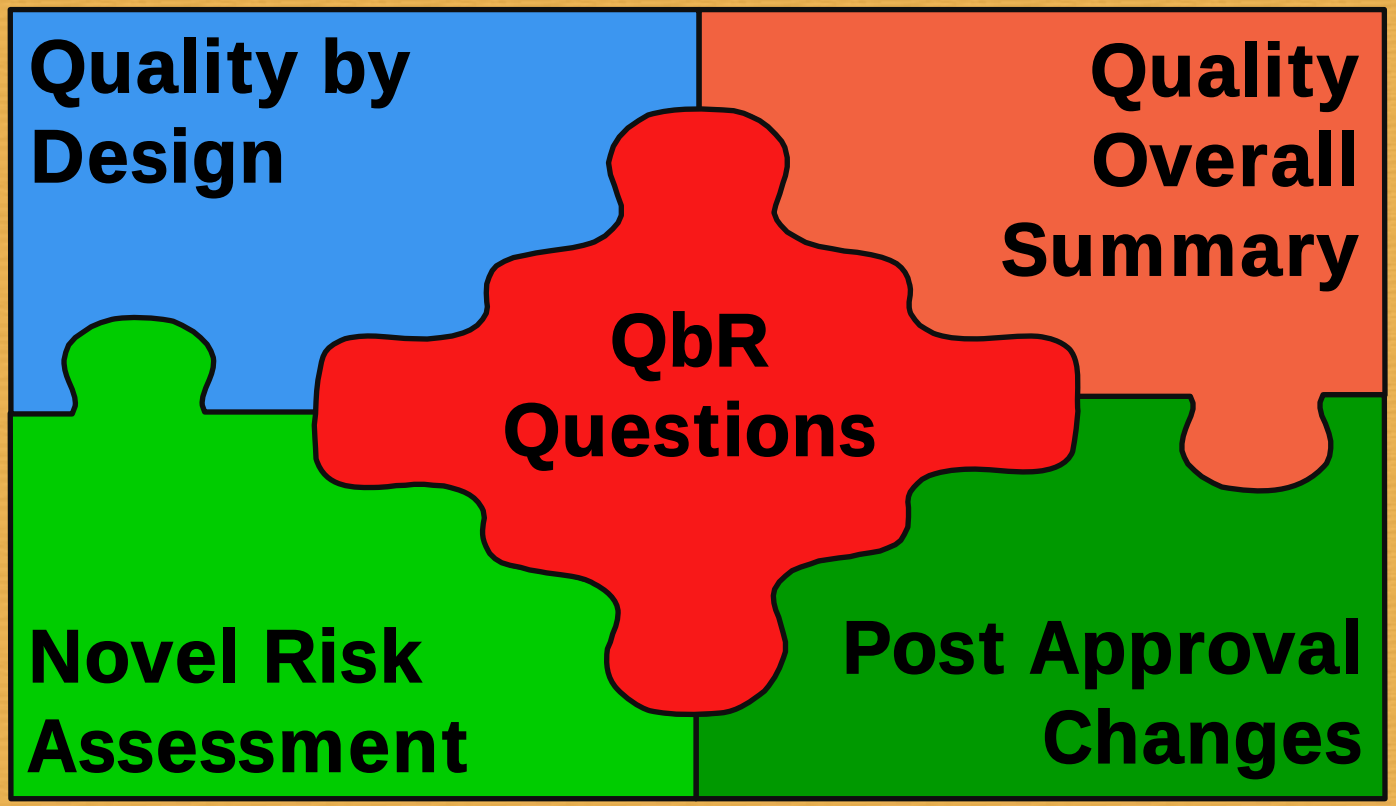
Why Question-based Review?

- Workload
  - Number of applications is quickly growing
  - Number of reviewers is slowly growing
  - Each application leads to supplements
- Quality
  - FDA cGMP Initiative; Pharmaceutical Quality in the 21st Century
  - Issues with current CMC review

Question-based Review

- Question-based Review is a new review system for a science and risk-based assessment of product quality
  - Contains the important scientific and regulatory review questions to
    - Comprehensively assess critical formulation and manufacturing process variables
    - Set regulatory specifications relevant to quality
    - Determine the level of risk associated with the manufacture and design of the product

Question-based Review System



Question-based Review Incorporates Quality by Design to Assure Product Quality

What is Quality?

- Fitness for intended use
  - Free of contamination and reproducibly deliver the therapeutic benefit promised in the label to the consumer (Janet Woodcock)
    - Consumer expectation
- Pharmaceutical Quality

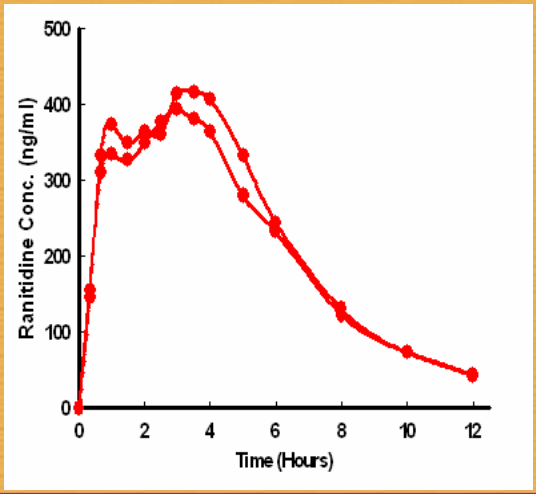
  $= f$ (drug substance, excipients, manufacturing)

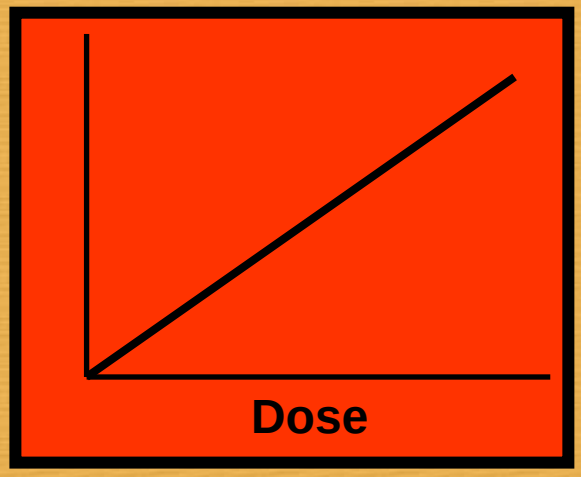
How Do You Judge Quality?

- Quality can be evaluated by in vivo or in vitro performance tests
  - In Vivo: PK, PD, Clinical
  - In Vitro: Assay, Uniformity, Purity, and/or Dissolution

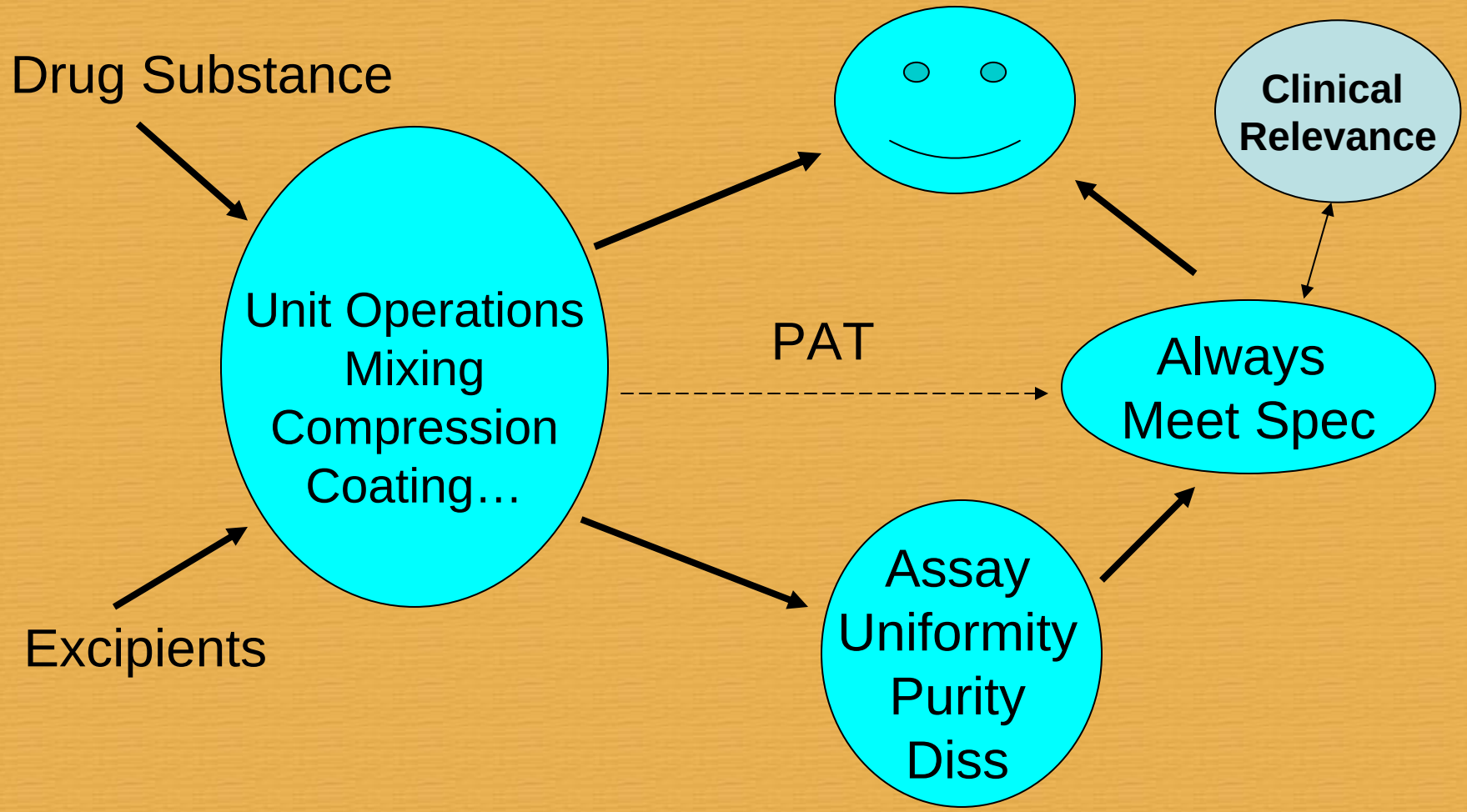
How Does Quality Relate to Product Performance?

- Quality by design assures *in vitro* product performance
- *In vitro* product performance provides assurance of *in vivo* product performance



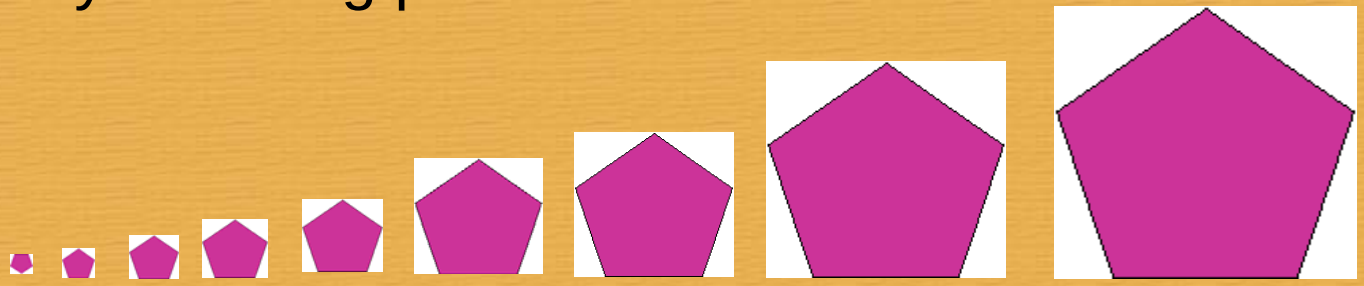


Quality by Design



What is Quality by Design?

- Pharmaceutical Quality by Design (QbD)
  - QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality
    - Understanding and controlling formulation and manufacturing process variables affecting the quality of a drug product



Where Does Design of Quality Begin?

- Target product quality profile
  - Beginning drug development with the end in mind
  - What performance is needed to get clinical benefit and meet consumer expectation
- Pharmaceutical Quality

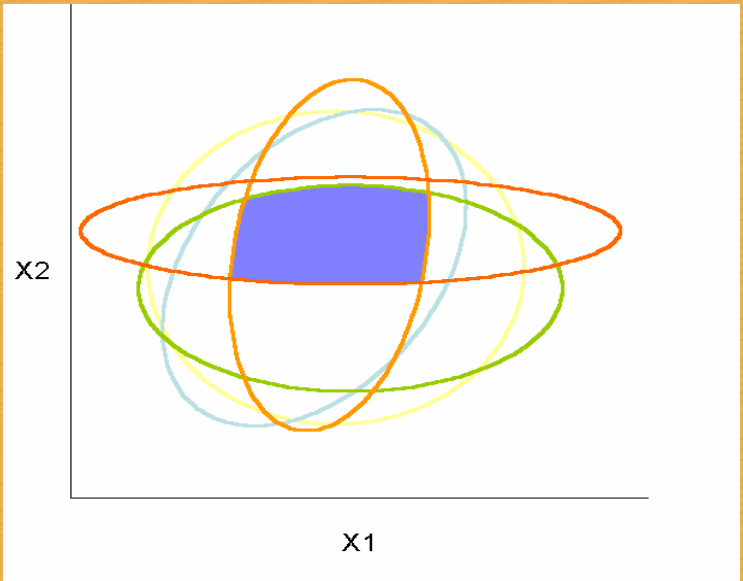
  $= f$ (drug substance, excipients, manufacturing)

What Does QbD Constitute?

- Define target product quality profile
  - The performance needed to get clinical benefit and meet consumer expectation
- Design and develop product and manufacturing process to meet target product quality profile
- Identify and control critical raw material attributes, process parameters, and sources of variability
- The process is monitored and adapted to produce consistent quality over time

Design Space

- Design Space
  - The multidimensional combination and interaction of input variables (eg. Material attributes) and process parameters that have been demonstrated to provide assurance of quality
- Design of Experiments
  - A structured, organized method for determining the relationship

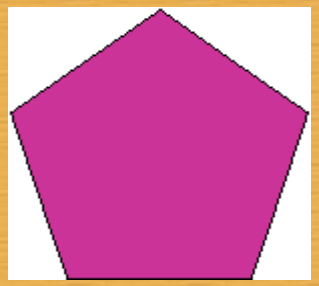


Design Space: Regulatory Challenges

10 Fold

Generation

Confirmation



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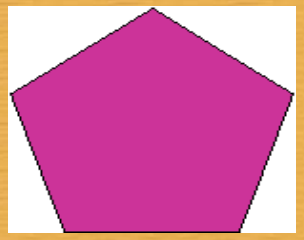


Potential Design Space

Design Space

QbD Questions Under QbR

- Define target product quality profile
  - What attributes should the drug product possess?
- Design and develop product and manufacturing process to meet target product quality profile
  - How was the product designed to have these attributes?
  - Were alternative formulations or mechanisms investigated?
  - How were the excipients and their grades selected?
  - How was the final formulation optimized?

QbD Questions Under QbR (Continued)

- Design and develop product and manufacturing process to meet target product quality profile
  - What are the unit operations in the drug product manufacturing process?
  - Why was the manufacturing process selected?
  - How are the unit operations related to the drug product quality?

QbD Questions Under QbR (Continued)

- Identify and control critical raw material attributes, process parameters, and sources of variability
  - Which properties or physicochemical characteristics of the drug substance affect drug product development, manufacture, or performance?
  - What evidence supports compatibility between the excipients and the drug substance?
  - How were the critical process parameters identified, monitored, and controlled?

QbD Questions Under QbR (Continued)

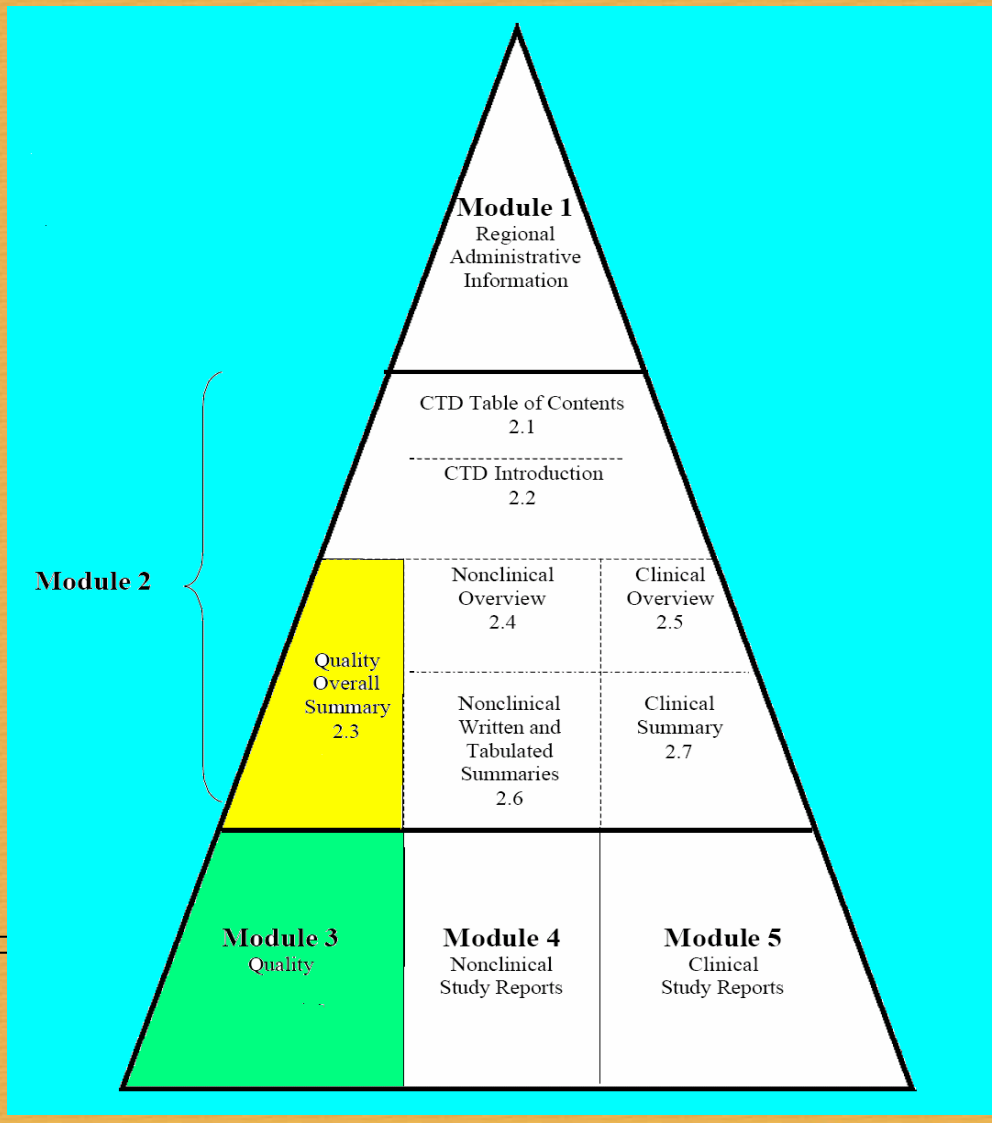
- The process is monitored and adapted to produce consistent quality over time
  - What are the in-process tests and/or controls that ensure each step is successful?
  - What is the scale-up experience with the unit operations in this process?
  - In the proposed scale up plan what operating parameters will be adjusted to ensure the product meets all in-process controls and final product specifications?
  - What evidence supports the plan to scale up the process to commercial scale?

Question-based Review Uses Quality Overall Summary to Ensure Efficient CMC Assessment

Diagram of the ICH Common Technical Document

QOS
Summary of Critical CMC Elements

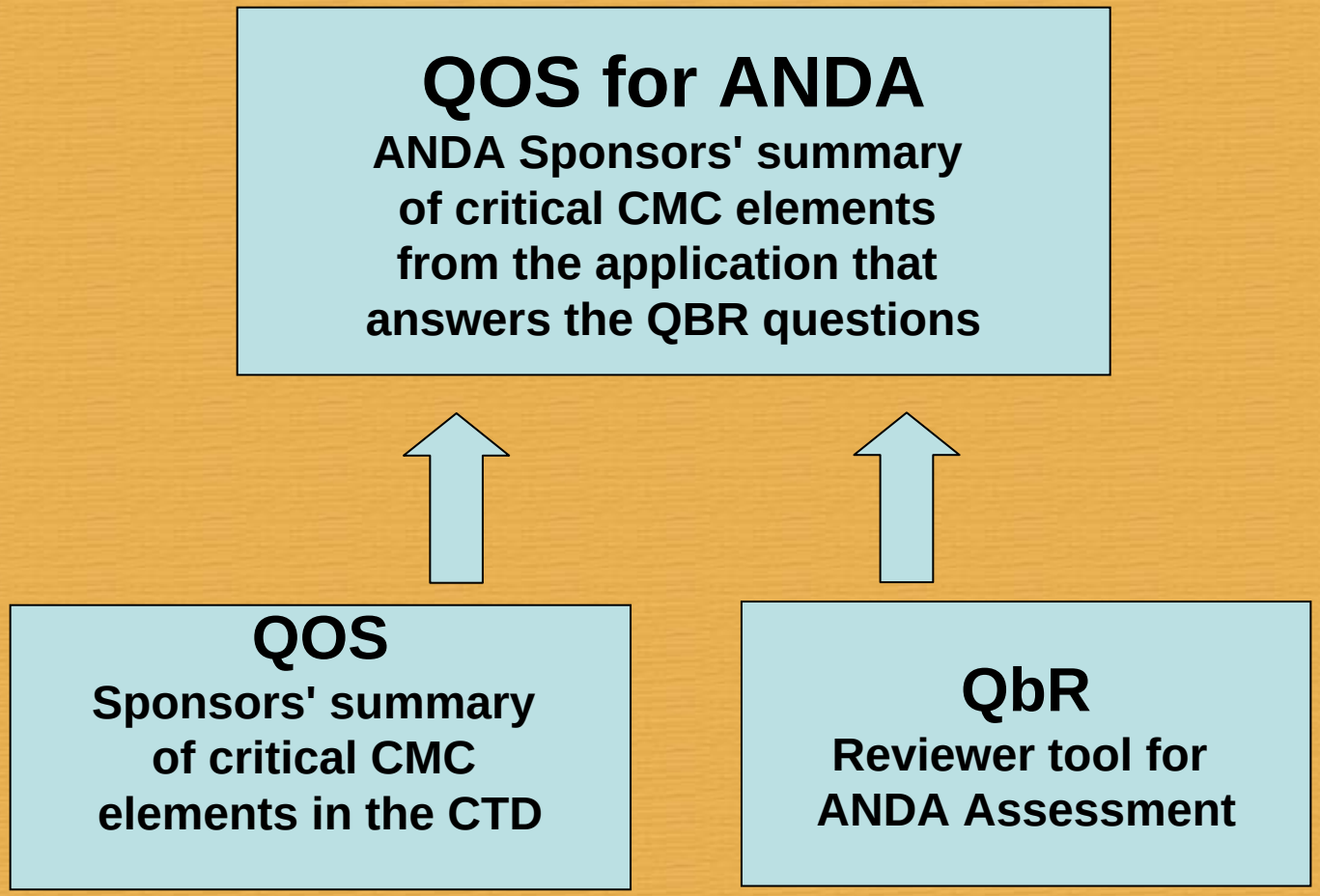
Body of Data
Detailed CMC Submission Package



ANDAs under QbR

- Encouraging all ANDAs be submitted in the CTD format and preferably electronic CTD to support Question-based Review
  - The 1999 and 2002 Guidances for Industry; Organization of an ANDA have been removed from the Regulatory Guidance page
  - The ANDA Checklist for Completeness and Acceptability of an Application for Filing can be found on the OGD web page (4/19/2006) http://www.fda.gov/cder/ogd/

QbR-QOS for ANDAs



OGD Model QOS

- Model Quality Overall Summary for ER Product
  - http: //www.fda.gov/cder/ogd/ OGD_Model_Quality_Overall_Summary.pdf
- Model Quality Overall Summary for IR Product
  - http: //www.fda.gov/cder/ogd/ OGD_Model_QOS_IR_Product.pdf

Quality Review under QbR

ANDA Application:
Electronic QOS (Module 2)
& Body of Data (Module 3)

Reviewer evaluates application to assess

- **Identity, strength, stability, purity, and quality**
- **Sponsor's identification and control of critical formulation and process variables**
- **Specifications**

Reviewer prepares critical assessment using QOS

If necessary, reviewer edits QOS:

- **Deletes superfluous information from QOS**
- **Rectify QOS by adding missing and essential information**

Quality review under QbR for Generic Drugs

QbR Uses QOS for Regulatory Assessment

- Quality Overall Summary that will
  - directly address OGD’s questions
  - result in a better understanding of sponsors' rationale for decisions and therefore, less misunderstandings
  - reduce reviewers' time spent in fact finding and summarizing ANDA elements

Question-based Review

Uses A Novel Risk-based Approach to Maximize Economy of Time, Effort, and Resources and to Facilitate Continuous Improvements

Risk-based Approach

- One goal of risk assessment is to allocate scarce reviewer resources to benefit the public
  - More emphasis on
    - Critical dose drugs (NTI)
    - “Complex” dosage forms/delivery systems
  - Less yet appropriate emphasis on
    - Solution products and Solid Oral IR Dosage Forms
  - Eliminating supplements for minor and most moderate and some major post-approval changes

Manufacturing Process Assessment

- Three-tiered assessment of manufacturing
  - Tier 1 applies to all dosage forms
  - Tier 2 applies to dosage forms that are not solutions (equivalent to current practice)
  - Tier 3 applies to dosage forms that are not solutions, IR tablets, or IR capsules

Post-approval Changes

- Draw conclusions about risk that will be useful in evaluating the need for post approval supplements
  - Eliminate/downgrade up to 80% of CMC supplements, and thus free up scarce resources
- Allow sponsors freedom to execute manufacturing processes for which they have demonstrated process understanding
  - Facilitating continuous CMC improvement and innovation

Proposed Risk-based Scoring System

- ANDA drugs: Risk score

NTI Drugs	+1
Complex dosage form	+1
Insufficient or missing PD reports	+1
Application of poor quality	+1

- Possible risk scores = 0, 1, 2, 3, or 4
- The review team proposes a final risk assessment score

What post-approval waivers/ commitments are appropriate?

- Total risk score of 1 or less
  - Many CBE-0 and CBE-30 changes shifted to annual report
  - Possible to downgrade certain PAS changes to CBE/annual report
- Total risk score of more than 1
  - No change in supplement submission and review

Question-based Review Will be Implemented in 2007

Question-based Review: Progress

2004	FDA's cGMP Initiative and Initiation of QbR
1/2005	QbR Questions drafted
2/2005	GPhA Technical Advisory Committee Meeting
4/2005	PQRI and FDA Specification Workshop
6/2005	OGD GPhA Technical Advisory Committee Joint Meeting
6/2005	GPhA Technical Advisory Committee Meeting
8/2005	OGD QbR White Paper
10/2005	AAPS Quality Workshop
10/2005	OGD GPhA Technical Advisory Committee Joint Meeting
10/2005	GPhA Fall Technical Workshop
1/2006	ANDA Submission Checklist
1/2006	Example Quality Overall Summary
2/2006	GPhA Technical Advisory Committee Meeting
3/2006	OGD CMC Review Format and Example
5/2006	GPhA QbR Training

QbR ANDA Submission

- Five major generic companies have submitted QbR applications
- Almost all major generic companies are planning to submit QbR applications this year

Experience with Assessment of QbR ANDAs: Documentation Advantages

- Primary reviewer saves time
  - Summary of application
    - Facts finding
    - Tables & charts
    - Chemical structures
    - Specifications etc
- No transcriptional errors

Experience with Assessment of QbR ANDAs: Technical Advantages

- Enhanced product and review assessment
  - Critical formulation and manufacturing process variables identified and controlled in QbR-QOS
- Insight into sponsor’s development plans
  - Product & Process Design and Development
  - Directly address the OGD’s questions
- Better understanding of sponsors' rationale for decisions and therefore, less misunderstandings

Question-based Review: Conclusion

- High product quality
  - Quality by design
- Efficient and timely review
  - Quality Overall Summary
- Risk based reduction of supplements
  - Up to 80% for ANDAs
- Science based specifications
  - Safety and efficacy, not process capability
- Consistency and transparency of review

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